HHS Public Access

Author manuscript

Int J Psychophysiol. Author manuscript; available in PMC 2022 February 23.

Published in final edited form as:

Int J Psychophysiol. 2021 December ; 170: 102–111. doi:10.1016/j.ijpsycho.2021.10.007.

Task switching reveals abnormal brain-heart electrophysiological signatures in cognitively healthy individuals with abnormal CSF amyloid/tau, a pilot study

Rebecca Johnson Arechavala[a], **Roger Rochart**[b], **Robert A. Kloner**[c,f], **Anqi Liu**[d,h], **Daw-An Wu**[e], **Shao-Min Hung**[e], **Shinsuke Shimojo**[e], **Alfred N. Fonteh**[b], **Michael T. Kleinman**[a], **Michael G. Harrington**[g], **Xianghong Arakaki**[b,*]

[a]University of California Irvine, Irvine, CA 92697-1830, USA

[b]Neurosciences, Huntington Medical Research Institutes, Pasadena, CA 91105, USA

[c]Cardiovascular Research, Huntington Medical Research Institutes, Pasadena, CA 91105, USA

[d]Department of Computing and Mathematical Sciences (CMS), California Institute of Technology, Pasadena, CA 91125, USA

[e]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA 91125, USA

[f]Division of Cardiovascular Medicine, Dept of Medicine, Keck School of Medicine at University of Southern California, Los Angeles, CA 90033, USA

[g]Neurology, Keck School of Medicine at University of Southern California, Los Angeles, CA 90033, USA

[h]Department of Computer Science, Whiting School of Engineering, Johns Hopkins University, Baltimore, MD 21218, USA

Abstract

Electroencephalographic (EEG) alpha oscillations have been related to heart rate variability (HRV) and both change in Alzheimer's disease (AD). We explored if task switching reveals altered alpha power and HRV in cognitively healthy individuals with AD pathology in cerebrospinal fluid (CSF) and whether HRV improves the AD pathology classification by alpha power alone.

We compared low and high alpha event-related desynchronization (ERD) and HRV parameters during task switch testing between two groups of cognitively healthy participants classified by CSF amyloid/tau ratio: normal (CH-NAT, n = 19) or pathological (CH-PAT, n = 27). For the task

*Corresponding author at: Neurosciences, Huntington Medical Research Institutes (HMRI), 686 South Fair Oaks Avenue, Pasadena, CA 91105, USA. xianghong@hmri.org (X. Arakaki).

CRediT authorship contribution statement

Conceived and designed the experiments: XA, MGH. Performed the experiments: XA MGH. Analyzed the data: RJA AL RR AF MK MGH XA. Wrote the paper: RJA AL RR XA. Edited the paper: RJA AL RR RK DW SH SS AF MK MGH XA. All authors contributed towards the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2021.10.007.

switching paradigm, participants were required to name the color or word for each colored word stimulus, with two sequential stimuli per trial. Trials include color (cC) or word (wW) repeats with low load repeating, and word (cW) or color switch (wC) for high load switching. HRV was assessed for RR interval, standard deviation of RR-intervals (SDNN) and root mean squared successive differences (RMSSD) in time domain, and low frequency (LF), high frequency (HF), and LF/HF ratio in frequency domain.

Results showed that CH-PATs compared to CH-NATs presented: 1) increased (less negative) low alpha ERD during low load repeat trials and lower word switch cost (low alpha: $p = 0.008$, Cohen's $d = -0.83$, 95% confidence interval −1.44 to −0.22, and high alpha: $p = 0.019$, Cohen's $d = -0.73$, 95% confidence interval −1.34 to −0.13); 2) decreasing HRV from rest to task, suggesting hyper-activated sympatho-vagal responses. 3) CH-PATs classification by alpha ERD was improved by supplementing HRV signatures, supporting a potentially compromised brain-heart interoceptive regulation in CH-PATs. Further experiments are needed to validate these findings for clinical significance.

Keywords

Task switching; Alzheimer's disease (AD); Cognitively healthy with normal (CH-NAT) or pathological (CH-PAT) cerebrospinal fluid (CSF) amyloid/tau; Electroencephalography (EEG); Alpha event-related desynchronization (ERD)

1. Introduction

1.1. Task switching

Cognitive flexibility refers to an individual's ability to switch between tasks. It is a core executive function that can be tested by task switching paradigms (Sauseng et al., 2006; Verstraeten and Cluydts, 2002). During task-switching, required efforts are typically greater on task switch trials (high load) compared to task repeat trials (low load), a phenomenon known as switch cost (Hsieh and Allport, 1994). In task-switching paradigms, response times (RTs) are typically longer on task switch trials compared to task repeat trials. Relatively less studied are greater cognitive efforts needed for switching trials than repeat tasks (Wu et al., 2015). Performance in task switching decreases in early AD (Hutchison et al., 2010). In addition, task switching is tightly linked with attention control modulated by proportion of switch/repeat trials (Schneider, 2015).

1.2. Alzheimer's disease, alpha event-related desynchronization (ERD), and cognitive challenge

Studies on early Alzheimer's disease (AD) or preclinical AD have been an active area of research due to the lack of effective treatment at the symptomatic stage (Barnett et al., 2014; Eikelboom et al., 2019). Changes in amyloid/tau and synaptic functions precede cognitive decline in AD by decades (Sperling et al., 2011). Synaptic dysfunction or abnormalities in cognition and cortical structures in early AD can be detected by electrophysiological methods, such as electroencephalogram (EEG) and/or electrocardiogram (ECG) (Babiloni et al., 2021; Lin et al., 2017; Zulli et al., 2005). Alpha band activity from quantitative

EEG (qEEG) has been complimentary to other AD measurements (Babiloni et al., 2015; Nakamura et al., 2018).

Alpha event-related desynchronization (ERD) responses have been considered as a functional correlate of brain activation (Klimesch, 2012; Klimesch et al., 2007), such that more negative alpha ERD refers to more brain activation, and less negative refers to less activation, or more efficient cognition (Grabner et al., 2004). Our previous studies have suggested that cognitively healthy (CH) elderly participants with pathological cerebrospinal fluid (CSF) β_{42}-amyloid/tau ratio (CH-PAT) compared to those with normal ratio (CH-NATs) were at higher risk of cognitive decline in a longitudinal follow up study (Harrington et al., 2019). With working memory and Stroop interference challenge, CH-PATs presented more negative alpha ERD than CH-NATs (Arakaki et al., 2020; Arakaki et al., 2019). Those results are consistent with poor performers and suggest compensatory hyperactivity (Grabner et al., 2004). Working memory and inhibitory control are required for task switching (Diamond, 2013; Pettigrew and Martin, 2016), both reduced in AD (Amieva et al., 2004a; Amieva et al., 2004b; Sullivan and Faust, 1993). Furthermore, alpha oscillation during task switching reveals general attention (low alpha) and task-specific attentional control (high alpha), and poor performers during task switching present increased (less negative) alpha ERD (Verstraeten and Cluydts, 2002).

1.3. Alpha oscillation, heart rate variability, and machine learning

Alpha oscillations have been related to heart rate variability (HRV) (analyzed from ECG) (Magosso et al., 2019), which both change in mild cognitive impairment (MCI) or AD (Babiloni et al., 2015; Nicolini et al., 2020).

HRV measures the balance of sympathetic and parasympathetic activities (Dziembowska et al., 2016; Prinsloo et al., 2013). HRV was analyzed as standard deviation of RR-intervals (SDNN) and root mean squared successive differences (RMSSD) in the time domain as well as high (HF) and low frequency (LF) in the frequency domain. Overall, RMSSD and HF reflect vagal inputs to the heart, and the sympatho-vagal balance is often expressed as the ratio of low- and high-frequency power (LF/HF). There are both structural and functional overlaps between HR regulation and executive functions (Forte et al., 2019a; Forte et al., 2019b; Kennelly et al., 2009). Alpha ERD correlates with HRV biomarkers of sympathetic (SDNN) and parasympathetic (RMSSD and HF) activity (Edlinger and Guger, 2005), which is regulated by prefrontal cortical activities in neurovisceral network (Thayer et al., 2009). Studies have linked the development of dementia with HRV (Kim et al., 2006; Nicolini et al., 2014). Furthermore, HRV biofeedback was associated with EEG changes suggesting increased internal attention and relaxation (Prinsloo et al., 2013). These studies supported brain-heart interoceptive connections in physiological and pathological conditions (Chen et al., 2021). Importantly, EEG/ECG has been considered candidates of “globally coupled oscillators” from holistic view (Basar, 2008). The interoceptive signatures are currently understudied in CH-PATs vs. CH-NATs.

1.4. Study summary

We aimed to reveal subtle synaptic dysfunction in the CH-PAT group by combining task switching challenge and qEEG. We aimed to explore whether low alpha and high alpha ERD increases (less negative) during low load repeat trials, high load switching trials, and switching cost in CH-PATs vs. CH-NATs. We explored if HRV would improve the classification of CH-PATs from CH-NATs by alpha ERD alone.

In sum, our overall aims of this pilot study in CH-PATs vs. CH-NATs included: i) We explored alpha ERD changes between two groups: low alpha and high alpha ERD changes during all trial types; during low load repeat trials and high load switching trials; and for switching cost. ii) We explored HRV changes between two groups in the time domain (SDNN and RMSSD) and frequency domain (LF, HF, and LF/HF). iii) We tested the hypothesis that supplementing HRV data improves classification of CH-PATs from CH-NATs by alpha ERD alone, using machine learning.

The lack of systematic approach to study preclinical AD is a problem. We planned this pilot study with the intention of acquiring data to generate future testable hypotheses. We will take an assumption-free approach, although we do have some general predictions.

2. Materials and methods

2.1. Participants

The Huntington Medical Research Institutes (HMRI) Institutional Review Board (IRB) approved this study (Quorum IRB, Seattle, Study # 27197) and all participants signed the consent form.

This is a pilot study based on a large ongoing aging cohort. All participants were recruited from advertisements in local newspapers and newsletters, the Pasadena Huntington Hospital Senior Health Network, the Pasadena Senior Center, and meetings with local physicians where we presented this research. They were classified as cognitively healthy (CH) after comprehensive neuropsychological battery in which testing was performed independently of the biochemical classification. Assessments included demographic data, medical history and physical exam, blood dementia screening, disease severity, disability scales, and CSF amyloid/tau measurements and Aβ/tau ratios (Harrington et al., 2013). We tested the cognitive domains of memory, executive function, language, attention, and visuospatial orientation, which were combined with Clinical Dementia Rating (CDR), Montreal Cognitive Assessment (MoCA), and Mini-Mental State Examination (MMSE), as previously described (Harrington et al., 2013).

Sixty-five cognitively healthy participants (51 to 91 years) participated in this pilot study. Ten participants were excluded from the study: 6 participants could not finish the whole task, finding it too challenging, and 4 participants had an accuracy lower than 25% (one out of four categories, procedure details in Section 2.2) or had repeat or switch accuracy lower than 50% (one out of two categories). We excluded the participants whose correct responses were no higher than odds of chance, because the participants are simply guessing but not actively engaging their cognitive resources to perform the best of their abilities.

Participants were then divided depending on individual CSF Aβ/tau ratios compared to a cutoff value derived from a logistic regression model that correctly diagnosed >85% of clinically probable AD participants (Harrington et al., 2013). A total of 55 study participants took part in the experiment: 23 CH-NATs and 32 CH-PATs. With large artifact rejection that described in Section 2.3 below and previously published (Arakaki et al., 2019), 46 participants' EEG were analyzed: 19 CH-NATs and 27 CH-PATs.

All behavioral and EEG data collection and processing was performed in a double blinded fashion with neither researchers nor participants knowing the CH-NAT/CH-PAT status.

2.2. Procedures

Study participants were seated in front of a desktop (a Dell Precision T5610 with a 20′′ screen) in a quiet room. For resting state, participants were asked to "sit still" and "empty their minds" for 5 min with their eyes open (eyes fixed at the 'E' of the DELL sign on the bottom of the dark screen), and then for 5 min with eyes closed.

For task switching testing, participants were comfortably seated before a computer screen and were instructed, practiced for ~5 min (or until satisfied with their performance), and then tested for task switching. The task switching paradigm was administered using E-prime software (Psychology Software Tools, Inc., Sharpsburg PA) on the same desktop. Each trial contained two sequential stimuli (both were incongruent colored words, e.g., 'Red' in green color and 'Green' in red color), which were displayed with or without an underline. Stimuli were 18 pt. Courier New font with black background (Fig. 1). Participants were required to name the color (c) when underlined or word (w) when not underlined for each stimulus by pressing a button: '1' for red and '2' for green. Thus, we divided the trials into low load repeat (color-color (cC) or word-word (wW)) or high load switching (cW or wC) trials (the second stimulus using superscript for the study target). Task switching included 3 mixed blocks of 64 trials in each block, including all four conditions (cC, wW, cW, wC) randomly sequenced and equally weighted. The task switching test took about 25 min to complete, depending on each participant's performance.

At the end of the experiment, participants filled a one-page survey to rate any physical complaints, difficulty of switch and repeat trials, how much effort they used, and how fatigue they felt after the task, on a sliding scale of 0–3.

2.3. Behavioral and qEEG analysis

The behavioral performances were described and compared by accuracy (ACC) and response time (RT): ACC was defined as the percentage of correctly responded trials out of the total trials, when responses to both stimuli of the trial were correct; RT was defined as the duration from the second stimulus onset to participant's response to the second stimulus. ACC and RT were compared between repeat trials and switch trials.

Online EEG data were collected during rest or cognitive challenge (Arakaki et al., 2018). Briefly, we used a 21-sensor, dry electrode system (Quasar Wearable Sensing, DSI-24, San Diego, CA) placed approximately at locations of the international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, M1, and M2) to

record EEG signals. EEG signals were sampled at 300 Hz, and bandpass filtered between 0.003 and 150 Hz. Three auxiliary sensors were used to record electrooculographic (EOG), electrocardiographic (ECG), and electromyographic (EMG) (on the right forearm) activities. A trigger channel encoded the presentation of the letter stimuli, the participants' responses, and the type of test (color-color, word-word, color-word, or word-color) for further analysis.

All datasets were analyzed in EEGLAB version 13.4.3b (Delorme and Makeig, 2004) running in MATLAB R2020a (The MathWorks, USA) and custom codes developed in-house. Preprocessing steps included epoching, filtering, re-referencing, large artifact removal, and time-frequency analysis. The continuous EEG recordings were segmented into epochs of 2500 ms duration during eyes open and eyes closed for resting state or using the stimulus onset as a reference during the task switching challenge, including 500 ms before and 2500 ms after stimulus onset. Only correctly responded trials (correctly responded to both stimuli of the trial) were used for analysis because we were interested in activities supported by the task switching.

Preprocessing and time-frequency (TF) analyses were carried out as previously described (Arakaki et al., 2018). Briefly, epochs were filtered between 2 and 30 Hz, re-referenced to the mean of two mastoid sensors (M1 and M2), and independent component analysis (ICA) was used to remove eye blinks, cardiac, and other artifacts (Delorme and Makeig, 2004). Trial with large artifact activity greater than three standard deviations (SDs) from a specific sensor's mean was consider a bad trial and rejected from all sensors. Nine participants with missing trials from any one category (cC, wW, cW, or wC) were removed for analysis. Therefore, average trials analyzed for all participants are 35 ± 4 (cC), 32 ± 7 (cW), 32 ± 6.7 (wW), and 31 ± 6 (wC). For TF analysis, epoched EEG data were decomposed with logarithmic scaling between 2 and 30 Hz by fast Fourier transform and Morlet wavelet $\left[e^{i2\pi t f}e^{-t2/2\sigma 2}\right]$ convolution in the frequency domain, followed by the inverse fast Fourier transform (Cohen, 2014; Cohen and Donner, 2013). Power values were normalized by decibels to the baseline power from −400 to −100 ms pre-stimulus at each frequency band $\left[dB\ power = 10 * log10\left(\frac{power}{baseline}\right)\right]$. Based on the TF plots and published data (Hu et al., 2013; Pagano et al., 2015; Vazquez-Marrufo et al., 2017), alpha ERD (range 250–750 ms) including low alpha (8–11 Hz) and high alpha (11–13 Hz) were then extracted for comparison across regions, condition, and groups.

We compared alpha power, including low alpha (8–11 Hz) and high alpha (11–13 Hz) between two CH groups from electroencephalogram (EEG) at six brain regions including frontal (F: F3, Fz, F4); central (C: C3, Cz, C4), parietal (P: P3, Pz, P4), left temporal (LT: F7, T3, T5), right temporal (RT: F8, T4, T6), and occipital (O: O1, O2) regions.

2.4. ECG and HRV analysis

ECG traces of 5 consecutive minutes were analyzed from participants at rest and during the tasks. Participants were excluded from analysis if they had atrial fibrillation or if more than 30% of consecutive data were missing due to poor signal quality. ECG traces from subgroups of CH-NAT and CH-PAT participants were screened, blind to their grouping, to remove ectopic beats, followed by identifying normal RR-intervals (NN) using the

AcqKnowledge software (BIOPAC Systems, Inc., Goleta, CA). Ectopic beats, including atrial premature beats, ventricular premature beats and skipped beats as well as atrial fibrillation were verified by a cardiologist who over-read the ECGs. HRV was analyzed following the established guidelines (1996). Using Kubios HRV software (version 3.2.0), NN intervals underwent linear interpolation (Choi and Shin, 2018) and subsequent analysis for the standard deviation of NN (SDNN) and root mean squared successive differences (RMSSD) in the time domain. Frequency domain measures were calculated after Fast Fourier Transform (FFT), specifically Welch's periodogram, to estimate the power spectral density. The LF and HF bands' thresholds are 0.04–0.15 Hz and 0.15–0.4 Hz, respectively. Heart rate and HRV parameters (RR, SDNN, RMSSD, LF and HF) were compared between CH-NATs and CH-PATs during rest or task.

For task-shifting, 5-minute ECG traces from CH-NATs (n = 19) and CH-PATs (n = 27) were analyze for HR and HRV measures at rest and during the task-shifting protocol.

2.5. Machine learning

We used machine learning methods to identify features that associate with the probability for distinguishing CH-NATs and CH-PATs, using low alpha ERD (6 brain regions during repeat and switch trials) and HRV measures (during resting and task). We also did a preliminary experiment to explore whether the features are contributing to the classification of CH-NATs and CH-PATs. For all the implementation, we utilized python codes developed in-house.

We first used linear logistic regression to demonstrate the feature significance. For linear logistic regression, we assume there is a linear relationship between the potential classifier variables X and the logit of the event Y. Here, our Y variables are the events of CH-NATs and CH-PATs, the potential classifier variables are the low alpha ERD over six brain regions and the HRV features during rest or tasks. If p is the probability of Y = CH-PATs, we have $log\frac{p}{1-p} = wX + b$, where w is the coefficient vector and b is the intercept. We can then tell from the sign of w to figure out whether a feature is positively or negatively associated with a classified event's probability. We repeated this experiment multiple times to determine whether the association is significant or not.

After identifying useful features, we tested whether HRV features help improve the machine learning model's classifying performance of CH-NATs versus CH-PATs. We used a two-layer, fully-connected neural network with 30 hidden nodes to build a binary classifier (CH-NATs vs. CH-PATs) on our selected features. We compare using only low alpha ERD (brain signatures), using only HRV features, and using both low alpha ERD and HRV features. In the training of the neural networks, we keep the hyperparameters the same for all the experiments.

2.6. Statistics

All tests were two-sided *t*-tests at a 0.05 significance level. All analyses were exploratory and thus there was no adjustment for multiplicity and there is no *priori* determination of sample size. However, we analyzed between two groups at each of the four trial types, low alpha and high alpha, and six regions with false discovery rate (FDR) for context.

A two-way ANOVA was used to test for behavioral differences (RT and ACC, respectively) between group and trial type (repeat, switch).

We compared low and high alpha ERD between two groups (CH-NATs and CH-PATs), including four different trials (wW, cC, cW, and wC), six brain regions (F, C, P, LT, RT, and O). We conducted *t*-tests for each comparison between CH-PAT and CH-NAT for trial type, regions, word switch cost etc. We used Cohen's equation $d = \frac{\mu_1 - \mu_2}{S}$ for effect size (ES) to examine the magnitude of difference between two groups (CH-NATs and CH-PATS), where (d) is the effect size, $\mu 1$ is the control mean, $\mu 2$ is the experimental mean, and S is the pooled standard deviation. The pooled standard deviation was calculated from pooled variance: $S^2 = \frac{(n-1)S_x^2 + (m-1)S_y^2}{n+m-2}$, where S^2 is the pooled variance, n being the sample size of group 1, S_x^2 is the standard deviation of group 1, m being the sample size of group 2, and S_y^2 being the standard deviation of group 2. We reported comparisons with medium and large Cohen's d (Sawilowsky, 2009). Confidence interval (95%) for Cohen's d was calculated: $\mathrm{CI} = \left(d - 1.96 * \sqrt{\frac{n1+n2}{n1*n2} + \frac{d^2}{2*(n1+n2)'}} + 1.96 * \sqrt{\frac{n1+n2}{n1*n2} + \frac{d^2}{2*(n1+n2)}} \right)$ (Wutzl et al., 2021).

We also compared low and high alpha ERD between the two groups in two different ways: 1) we compared alpha ERD during repeat trials (low load) and switch trials (high load); 2) we compared alpha power for word switch cost (cW-wW) and color switch cost (wC-cC).

For HRV comparisons, we used a student two-sided *t*-test to compare between CH-NATs and CH-PATs with respect to time-domain and frequency-domain HRV measures. We also compared between resting and task state for each group.

We performed all analyses using PRISM v6.07 (GraphPad), MATLAB R2020a, or Excel from Microsoft Office 365. We set a significance level of 0.05 for all tests.

3. Results

3.1. Demographic balanced groups and resting alpha power between CH-NATs and CH-PATs

Demographic and cognitive screening measures were descriptively similar between CH-NATs and CH-PATs while CSF Aβ/tau ratios differentiate the two groups (Table S1). Furthermore, survey results showed no differences between two groups in physical complaints, difficulty of switch and repeat trials, effort used, and fatigue after the task.

We did not observe differences in alpha power during *resting eyes open* or *eyes closed* states between the two groups.

3.2. Behavioral performance, low and high alpha ERD during wW, cC, cW, and wC trials between CH-NATs and CH-PATs

For RT comparison, there was a significant main effect of trial types (repeat or switch), $F(1, 108) = 20.06$, $p < 0.0001$, with faster reaction time during repeat trials (mean: 1260.9 ms,

SD: 338.8 ms) than during switch trials (mean: 1606.6 ms, SD: 445.8 ms). However, there was no Group × trial type interaction, F(1, 108) = 0.0001, p = 0.991 (Fig. 2).

For ACC comparison, there was a significant main effect of trial types (repeat or switch), F(1, 108) = 4.01, p = 0.048, with higher ACC during repeat trials (mean: 0.89, SD: 0.12) than during switch trials (mean: 0.84, SD: 0.15). However, there was no Group × trial type interaction, F(1, 108) = 0.003, p = 0.960.

For comparisons of low and high alpha ERD during wW, cC, cW, and wC trials between the two groups, we did not observe significant p values that met FDR. The summary effect sizes for all comparisons were shown in Fig. 3. Specifically changing from CH-NATs to CH-PATs, there was a large effect size for central low alpha during wW trials (p = 0.005, df = 41, Cohen's d = 0.89, 95% confidence interval 0.28–1.51); several medium effect sizes during wW trials for parietal low alpha (p = 0.015, df = 39, Cohen's d = 0.76, 95% confidence interval 0.15–1.36), central high alpha (p = 0.025, df = 41, Cohen's d = 0.70, 95% confidence interval 0.09–1.30) (Table S2a–d).

We analyzed the alpha ERD during the repeat trials (wW&cC) and switch trials (cW&wC), or for word switch cost (cW-wW) and color switch cost (wC-cC). We did not observe significant p values that met FDR. Detailed results listed in Sections 3.3 and 3.4.

3.3. Low and high alpha ERD during low load (repeat trials, wW&cC) and high load (switch trials, cW&wC), between CH-NATs and CH-PATs

During repeat trials, low alpha power was increased (less negative) in CH-PATs than CH-NATs (Central: −0.18 ± 0.66 vs. −0.72 ± 0.72, p = 0.011, df = 37, Cohen's d = 0.79, 95% confidence interval 0.18–1.40; Parietal: −0.25 ± 0.75 vs. −0.83 ± 0.92, p = 0.024, df = 34, Cohen's d = 0.70, 95% confidence interval 0.09–1.30) (Table 1). The low alpha differences during repeats trials likely came from wW, but not cC (Section 3.2 and Table S2). During switch trials, we did not observe differences in low alpha or high alpha between two groups. There were no differences in other frequency powers (delta, theta, beta) (Table S3a–b).

3.4. Low and high alpha ERD for word switch cost (cW-wW) and color switch cost (wC-cC), between CH-NATs and CH-PATs

For word switch cost, we observed decreased low alpha ERD in CH-PATs compared to CH-NATs (Central: −0.12 ± 0.66 vs. 0.43 ± 0.68, p = 0.008, df = 38, Cohen's d = −0.83, 95% confidence interval −1.44 to −0.22), and decreased high alpha ERD in CH-PATs compared to CH-NATs (Central: −0.12 ± 0.49 vs. 0.32 ± 0.74, p = 0.019, df = 29, Cohen's d= −0.73, 95% confidence interval −1.34 to −0.13) (Tables 2). The low alpha differences for word switch cost likely came from wW, but not cW (Section 3.2 and Table S2). For color switch cost, we did not observe difference in low or high alpha ERD between the two groups.

3.5. HRV during resting and task

We observed no statistically significant changes in discrete HR or HRV measures between CH-NATs and CH-PATs at either time point. However, we observed significant HRV

changes, specifically a drop in LF ($p = 0.023$, Cohen's $d = -0.45$), within the CH-PAT group between the resting and task states, but none in CH-NATs ($p = 0.495$, Cohen's $d = -0.21$). A trend in SDNN suggested a drop during task shifting in CH-PATs ($p = 0.091$, Cohen's $d = -0.23$), while there was no change in CH-NATs ($p = 0.64$, Cohen's $d = -0.08$). Both groups exhibited a drop in RR interval while performing the task, with larger effect size drop in CH-PATs ($p = 0.0003$, Cohen's $d = -0.62$) than CH-NATs ($p = 0.028$, Cohen's $d = -0.24$) (Fig. 4, Table 3).

Atrial fibrillation, which led to exclusion from HRV analyses, was present in both CH-NATs ($n = 2$, 11% of participants) and CH-PATs ($n = 3$, 11% of participants) with no difference between groups. Ectopic beat prevalence showed no significant difference between CH-NATs and CH-PATs in the average number of total arrhythmias (Rest: 12.6 ± 18.9 vs. 12.4 ± 21.3, $p = 0.985$; Task: 7.8 ± 7.6 vs. 11.4 ± 30.6, $p = 0.731$), nor when separated by classification of arrhythmia as atrial premature beats (Rest: 6.0 ± 8.7 vs. 5.1 ± 10.9, $p = 0.892$; Task: 3.8 ± 6.2 vs. 1.2 ± 0.4, $p = 0.386$) and ventricular premature beats (VPB), where only one CH-PAT had VPB at rest (Rest: 16.0 ± 24.8 vs. 58.0; Task: 8.0 ± 7.2 vs. 19.4 ± 41.1, $p = 0.558$).

3.6. Machine learning to explore ECG features improve qEEG's classification of AD pathology

Our repeated 50 experiments on the low alpha features demonstrate that six low alpha features (Cr, Pr, LTr, Or, LTs, RTs: 'r' for repeat trials and 's' for switch trials) were considered significant between CH-NATs and CH-PATs. For HRV measures during rest (R) and task switching (TS), nine HRV features (MeanRR(R), SDNN(R), MeanHR(R), LF(R), MeanRR(TS), SDNN(TS), MeanHR(TS), LF/HF(TS), HR(R)) were considered significant between CH-NATs and CH-PATs in the 50 repeated experiments. The experiment was conducted with random splits of training (80%) and testing (20%) data.

We used a two-layer fully connected neural network to build a binary classifier (CH-NATs vs. CH-PATs) on our selected features. We compared using only low alpha ERD versus low alpha ERD and HRV features. Our result shows that the test accuracy was improved from 0.64 ± 0.04 to 0.71 ± 0.04. by supplementing the binary classifier with heart signatures (HRV) (Fig. 5). On the other hand, the heart feature can also achieve 0.62 ± 0.04 accuracy.

4. Discussion

The present pilot EEG/ECG study was designed to explore the changes of neural and cardiac electrophysiological signatures that associate with task switching in cognitively healthy individuals with pathological versus normal CSF amyloid/tau. Our results suggested that CH-PATs present increased (less negative) centroparietal alpha ERD during wW repeat trials compared to CH-NATs: on the one hand, low alpha ERD was increased (less negative) during low load repeat trials at centroparietal locations; on the other hand, central low alpha ERD was lower for word switch cost. Moreover, HRV measurements suggested that while RR drops in both groups (more so in CH-PATs), LF-HRV dropped from resting to task only in CH-PATs. Finally, supplementing the binary classifier with HRV signatures improved low alpha ERD's differentiation of CH-PATs from CH-NATs. In sum, task switching challenge

revealed the abnormal EEG/ECG signatures in CH-PATs compared to CH-NATs and their combination improves CH-PAT classification.

The CSF tau (t- or p-Tau)/Abeta ratio has been shown to predict cognitive decline in preclinical AD (Fagan et al., 2007), to predict MCI progression to AD (Ritchie et al., 2017), and to outperform amyloid or tau alone in discriminating those with cortical amyloid pathology (Fagan et al., 2011). Not focused on dementia types based on AT(N) research framework (Jack et al., 2018), we explored non-invasive EEG/ECG technology combined with cognitive challenge (task switching challenge in this study) to detect synaptic dysfunction in CH-PATs based on A/T ratio (Harrington et al., 2013; Harrington et al., 2019; Sperling et al., 2011).

4.1. Abnormal task switching (behavioral performance and alpha ERD) in AD spectrum

Working memory maintains the task set rules, and cognitive control helps resolve the conflict between competing task sets. Our previous study revealed that alpha ERD was more negative in CH-PATs than CH-NATs, suggesting compensatory hyperactivity or greater effort by the CH-PATs (Arakaki et al., 2020; Arakaki et al., 2019). Alpha ERD during working memory reflect cortical activation and neural efficiency, such that good performers present increased (less negative) alpha ERD (Grabner et al., 2004). On the other hand, alpha ERD during task switching reflect alertness (low alpha) and attention (high alpha), such that good performers present decreased (more negative) alpha ERD (Verstraeten and Cluydts, 2002). Therefore, we predict increased (less negative) alpha ERD in CH-PATs compared to CH-NATs during task switching.

While the brain can successfully alternate or shift its attention between tasks, the consistent mental replacement of one task by another requires effort (time and/or cognitive resources) for the brain to process, causing switching cost (Gladwin and de Jong, 2005; Jersild, 1927; Monsell, 2003; Wu et al., 2015). In our study, both groups exhibited longer RT during switch than repeat trials, indicating a successful switching cost effect.

Alpha ERD represents a short, localized, amplitude attenuation of alpha band oscillations (Pfurtscheller and Aranibar, 1977; Pfurtscheller and Klimesch, 1992). Alpha desynchronization has been observed during cognitive and attentional tasks in visual and auditory modalities (Klimesch, 1996, 1997; Krause et al., 1996). Low alpha (8–11 Hz) has been shown to be associated with general attention, whereas high alpha (11–13 Hz) is found to be associated with task-specific attention (Pfurtscheller and Lopes da Silva, 1999; Verstraeten and Cluydts, 2002). In our study, CH-PATs have increased (less negative) low alpha ERD compared with CH-NATs in the centroparietal regions during repeat trials, consistent with previous findings of poor performers, suggesting less attentive/alert (Verstraeten and Cluydts, 2002). The centroparietal location is consistent with a context update (Donchin and Coles, 1988), or the interference of processing the second stimulus from the previously activated task-set (Wu et al., 2015). This increased low alpha could result from mind wandering, as previous studies have shown an increase of alpha power constituting an electrophysiological correlate of mind wandering (Arnau et al., 2020; Compton et al., 2019).

Our findings are inconsistent with previous findings showing decreased low alpha ERD (more negative) in cW trials relative to wW trials (Wu et al., 2015), that is possibly due to our elderly participants being overtaxed by the switching trials.

Two neural processes underlying switch cost include endogenous control (color switch cost) and inhibitory control (word switch cost) (Wu et al., 2015; Yeung and Monsell, 2003). Our data indicated that the low and high alpha processing of word switch cost were smaller in CH-PATs, which appears counterintuitive. The reason could be that word switching cost differences mainly came from wW, not cW (overtaxed for both groups). Our data suggest that top-down inhibitory control was impaired in CH-PATs.

As reports of alpha ERD sometimes seem to conflict, please note that alpha ERD is a negative number in recent papers (including our calculation in decibels) (Wu et al., 2015) but positive in earlier studies, from different way of calculate (Klimesch et al., 1997). Another point worth notice is that CH-PATs presented decreased (more negative) alpha ERD during working memory and Stroop (Arakaki et al., 2020; Arakaki et al., 2019), however increased (less negative) alpha ERD during task switching in this study. This can be interpreted by the following possibilities: a) task switching is more challenging compared to working memory and Stroop, where CH-PATs presented compensatory hyperactivity during low load working memory and Stroop challenge, however already overtaxed during low load task switching challenge; b) weakened top-down inhibitory control in CH-PATs may result in hyperactivities (Stroop and working memory) and under-controlled cognitive flexibility (less negative alpha ERD) during low load trials. The CH-PATs' less negative alpha ERD during low load task switching challenge is consistent with poor performers (Verstraeten and Cluydts, 2002).

We mainly examined alpha ERD in this study, as alpha is the most prominent EEG band and changes in AD (Babiloni et al., 2021) as well as in CH-PATs (Arakaki et al., 2019). We did not observe changes in CH-PATs regarding other frequency bands.

4.2. Abnormal HRV in AD spectrum

Autonomic health when studied in AD patients, shows sympathetic dominance and parasympathetic suppression (Issac et al., 2017), in MCI participants, shows an orthosympathetic dysfunction (Nicolini et al., 2014). In addition, the prevalence of cognitive impairment was higher in those with reduced HRV than in those with nonreduced HRV (Kim et al., 2006). Further, HRV biofeedback (aiming to induce a respiratory sinus arrythmia peak) resulted in: LF HRV and SDNN increase and EEG changes suggestive of increased attention/relaxation (Prinsloo et al., 2013).

We observed contrasting LF responses to task switching by CH-NATs and CH-PATs indicate a possible imbalance in sympathetic and parasympathetic function in CH-PATs (Hayano and Yuda, 2019). The LF regulations are complex such that higher LF has been related to: respiration decreases to the resonance frequency (6 cycles/min) (Brown et al., 1993); younger age (middle to older population) (Jandackova et al., 2016); sitting position compared to supine and prone positions (Watanabe et al., 2007); and higher MoCA score (Frewen et al., 2013). Our two groups are similar in age, position, MoCA, thus

breathing will be an interesting factor to control for. In addition, anatomically besides the neurovisceral network (Thayer and Lane, 2009), a possible area of interest is the fornix of the hippocampus which serves as the predominant outflow tract of the hippocampus known to be implicated in autonomic control (Castle et al., 2005; Mielke et al., 2012). Disrupted functions in these areas may account for the depressed LF-HRV responses upon the task in CH-PATs. Further studies to stratify HRV changes by these factors and to localize the regulation of the early brain-heart dysfunctions will further advance our understanding.

The LF-HRV drop in CH-PATs from rest to task could be from both vagal and sympathetic decreases, which may link to decreased cardiac vagal control and healthy variability (Laborde et al., 2018; Shaffer and Meehan, 2020). Indeed, vagal tank theory proposes that cardiac vagal control is a physiological indicator reflecting self-regulation, such that the interaction of resting and reactivity (upon task) can predict latent abnormalities (Laborde et al., 2018). Interestingly, Nicolini et al. have shown that MCI participants presented less LF, HF, LF/HF changes in response to active standing than controls, but no HRV differences during baseline (Nicolini et al., 2014). The differences in theirs (less HRV changes in MCI) and our study (more HRV changes in CH-PATs) can be partly due to physical (positional) or mental (cognitive) challenges (Laborde et al., 2018). Overall, our data indicated hyper-responsive autonomic regulation in CH-PATs compared to CH-NATs, probably resulting from weakened top-down control (Thayer et al., 2009).

4.3. Machine learning and abnormal brain-heart in AD spectrum

Machine learning analysis supports that supplementing HRV improved low alpha in the classification of CH-PATs from CH-NATs, suggesting related changes in this early stage. Although the test accuracy is relatively low (from 0.64 ± 0.04 to 0.71 ± 0.04), our CH-NAT/CH-PAT classifier exploration is encouraging that combining EEG/ECG can improve CH-PAT classification. The feature significance using linear logistic regression is discussed in various previous literature (Bishop, 2006). Training neural networks (Goodfellow et al., 2016) to model the nonlinearity in the data is a prevalent practice. Note that we use different models for feature significance measurement and the classification task. The reason is that the feature importance is more meaningful when we assume a linear model. However, a non-linear model is required to achieve a better classifier performance in practice, consistent with the complex neurovisceral network (Thayer and Lane, 2009). Even though the final sensitivity and specificity is lower than expected 80%, possibly from our relatively small dataset in this preliminary study, our result suggest that the detection of CH-PATs by low alpha ERD alone is improved by supplementing HRV measures, supporting the interaction of alpha ERD and HRV during different stages, corroborate the vagal tank theory (Laborde et al., 2018). In the future work, we plan to test the effectiveness of HRV features on larger datasets.

There are anatomical and functional links between the brain and the heart allowing dynamic mutual influences and interoception (Chen et al., 2021). For example, increased risks of dementia related to: clinical stroke (de Bruijn and Ikram, 2014; Leys et al., 2005; Vermeer et al., 2003a); minor infarct (lacunae) (Vermeer et al., 2003a; Vermeer et al., 2003b); and atrial fibrillation (de Bruijn and Ikram, 2014; Ott et al., 1997). However, our present study did not

find atrial fibrillation differences between the two groups. That could be our relatively small sample size. The interoceptive relationship between the brain and the heart is intriguing and will benefit from non-invasive, translational studies that allow computer-aided approaches to help extract patterns from the dataset and detect individuals with high risk of AD (Leuzy et al., 2018). That is consistent with Dr. Basar's proposal for brain-body-mind incorporation from "globally coupled oscillators" (Basar, 2005, 2008). Although with limitations, we have explored through the lens of brain-heart electrophysiology to identify potential biomarkers (qEEG and ECG/HRV) for individuals who are cognitively healthy but with AD biomarkers (CH-PATs).

4.4. Significance of our findings

Our pilot study showed subtle changes in EEG and ECG/HRV in CH-PATs: task switching challenge revealed less negative alpha ERD during wW repeats. In our exploratory study, the trained binary classifier of CH-PATs from EEG/ECG helps better understand the change of brain-heart function in CH-PATs. Our task shifting paradigm combined with non-invasive EEG/ECG measures has shown evidence of an early association between cardiac vagal control and its link to cognitive health, in our initial studies.

4.5. Limitations and future directions

This initial study is exploratory in nature and has limitations due to its relatively small sample size; it was intended to help identify future hypotheses which we have discussed. Firstly, we did many tests and found no significant results after applying FDR for all alpha ERD comparisons between the two groups. All analyses were exploratory and thus there was no adjustment for multiplicity (alpha ERD and HRV analysis). We cannot exclude type 1 error at this stage. Larger population is needed to confirm our findings. Secondly, our cohort was primarily homogenous consisting mainly of Caucasian females of European descent. Recruitment for future studies will better balance sex while including a more diverse group of participants from various racial and ethnic backgrounds. Nevertheless, both CH-NATs and CH-PATs were age and sex-matched between the two groups in the present study indicating that these variables did not skew our results. Thirdly, our study shows high temporal resolution using qEEG to detect dysfunctions with accurate temporal precision. However, future studies that explore dysfunction in CH-PATs with higher spatial accuracy than the present study may help elucidate which regions are affected. Furthermore, the improving classification performance by supplementing HRV signatures may not be sufficient to demonstrate the direct brain-heart interoceptive activity. Additional approaches, such as fMRI to measure brain oxygen level during rest and task, are needed to provide direct support. Finally, we are planning a more extensive follow-up study of our results to help evaluate further whether these findings might have clinical significance and to confirm that our findings are replicable in a larger cohort.

5. Conclusions

This pilot study evaluated subtle changes of brain-heart interoception to help identify AD pathology in CH-PATs from CH-NATs. We found increased alpha ERD (less negative) during the word repeat trials and reduced LF-HRV from rest to task in CH-PATs vs.

CH-NATs. In addition, we have shown that combining both alpha ERD and HRV features increases the classification performance of alpha ERD alone in detecting CH-PATs. However, due to limited sample size, further experiments are needed to validate these findings. Nonetheless, our task switching paradigm combined with EEG/ECG has suggested a potentially compromised brain-heart interoception in CH-PATs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Betty Chung and David Buennagel assisted with participant recruitment. We thank the study participants for their altruistic participation in this research. We thank Dr. Janice Pogoda for statistical help. Cathleen Molloy helped with edits. Some data relied upon in this study was derived from research performed at HMRI by Dr. Michael G. Harrington.

Funding

This work was supported by National Institute on Aging [grant number R56AG063857, R01AG063857] and L. K. Whittier Foundation.

References

Amieva H, Lafont S, Rouch-Leroyer I, Rainville C, Dartigues JF, Orgogozo JM, Fabrigoule C, 2004a. Evidencing inhibitory deficits in Alzheimer's disease through interference effects and shifting disabilities in the Stroop test. Arch. Clin. Neuropsychol 19, 791–803. [PubMed: 15288332]

Amieva H, Phillips LH, Della Sala S, Henry JD, 2004b. Inhibitory functioning in Alzheimer's disease. Brain 127, 949–964. [PubMed: 14645147]

Arakaki X, Shoga M, Li L, Zouridakis G, Tran T, Fonteh AN, Dawlaty J, Goldweber R, Pogoda JM, Harrington MG, 2018. Alpha desynchronization/synchronization during working memory testing is compromised in acute mild traumatic brain injury (mTBI). PLoS One 13, e0188101. [PubMed: 29444081]

Arakaki X, Lee R, King KS, Fonteh AN, Harrington MG, 2019. Alpha desynchronization during simple working memory unmasks pathological aging in cognitively healthy individuals. PLoS One 14, e0208517. [PubMed: 30601822]

Arakaki X, Hung S, Wei K, Tran T, Arechavala R, Kleinman M, Kloner R, Fonteh A, King K, Harrington M, 2020. A study of alpha desynchronization, heart rate, and MRI during stroop testing unmasks pre-symptomatic Alzheimer's disease. Alzheimers Dement 16.

Arnau S, Loffler C, Rummel J, Hagemann D, Wascher E, Schubert AL, 2020. Inter-trial alpha power indicates mind wandering. Psychophysiology 57, e13581. [PubMed: 32277853]

Babiloni C, Del Percio C, Boccardi M, Lizio R, Lopez S, Carducci F, Marzano N, Soricelli A, Ferri R, Triggiani AI, Prestia A, Salinari S, Rasser PE, Basar E, Fama F, Nobili F, Yener G, Emek-Savas DD, Gesualdo L, Mundi C, Thompson PM, Rossini PM, Frisoni GB, 2015. Occipital sources of resting-state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 36, 556–570. [PubMed: 25442118]

Babiloni C, Arakaki X, Azami H, Bennys K, Blinowska K, Bonanni L, Bujan A, Carrillo MC, Cichocki A, de Frutos-Lucas J, Del Percio C, Dubois B, Edelmayer R, Egan G, Epelbaum S, Escudero J, Evans A, Farina F, Fargo K, Fernandez A, Ferri R, Frisoni G, Hampel H, Harrington MG, Jelic V, Jeong J, Jiang Y, Kaminski M, Kavcic V, Kilborn K, Kumar S, Lam A, Lim L, Lizio R, Lopez D, Lopez S, Lucey B, Maestu F, McGeown WJ, McKeith I, Moretti DV, Nobili F, Noce G, Olichney J, Onofrj M, Osorio R, Parra-Rodriguez M, Rajji T, Ritter P, Soricelli A, Stocchi F, Tarnanas I, Taylor JP, Teipel S, Tucci F, Valdes-Sosa M, Valdes-Sosa P, Weiergraber M, Yener G,

Guntekin B, 2021. Measures of resting state EEG rhythms for clinical trials in Alzheimer's disease: recommendations of an expert panel. Alzheimers Dement 17 (9), 1528–1553. 10.1002/alz.12311. [PubMed: 33860614]

Barnett JH, Lewis L, Blackwell AD, Taylor M, 2014. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. BMC Neurol 14, 101. [PubMed: 24885474]

Basar E, 2005. Memory as the "whole brain work": a large-scale model based on "oscillations in super-synergy". Int. J. Psychophysiol 58, 199–226. [PubMed: 16168506]

Basar E, 2008. Oscillations in "brain-body-mind"—a holistic view including the autonomous system. Brain Res 1235, 2–11. [PubMed: 18638460]

Bishop CM, 2006. Pattern Recognition and Machine Learning Springer, New York.

Brown TE, Beightol LA, Koh J, Eckberg DL, 1993. Important influence of respiration on human R-R interval power spectra is largely ignored. J. Appl. Physiol. (1985) 75, 2310–2317. [PubMed: 8307890]

Castle M, Comoli E, Loewy AD, 2005. Autonomic brainstem nuclei are linked to the hippocampus. Neuroscience 134, 657–669. [PubMed: 15975727]

Chen WG, Schloesser D, Arensdorf AM, Simmons JM, Cui C, Valentino R, Gnadt JW, Nielsen L, Hillaire-Clarke CS, Spruance V, Horowitz TS, Vallejo YF, Langevin HM, 2021. The emerging science of interoception: sensing, integrating, interpreting, and regulating signals within the self. Trends Neurosci 44, 3–16. [PubMed: 33378655]

Choi A, Shin H, 2018. Quantitative analysis of the effect of an ectopic beat on the heart rate variability in the resting condition. Front. Physiol 9, 922. [PubMed: 30050470]

Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93, 1996, 1043–1065. [PubMed: 8598068]

Cohen MX, 2014. Analyzing Neural Time Series Data: Theory and Practice

Cohen MX, Donner TH, 2013. Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. J. Neurophysiol. 110, 2752–2763. [PubMed: 24068756]

Compton RJ, Gearinger D, Wild H, 2019. The wandering mind oscillates: EEG alpha power is enhanced during moments of mind-wandering. Cogn. Affect. Behav. Neurosci 19, 1184–1191. [PubMed: 31502206]

de Bruijn RF, Ikram MA, 2014. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med 12, 130. [PubMed: 25385322]

Delorme A, Makeig S, 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134, 9–21. [PubMed: 15102499]

Diamond A, 2013. Executive functions. Annu. Rev. Psychol 64, 135–168. [PubMed: 23020641]

Donchin E, Coles M, 1988. Is the P300 component a manifestation of context updating. Behav. Brain Sci 11, 71.

Dziembowska I, Izdebski P, Rasmus A, Brudny J, Grzelczak M, Cysewski P, 2016. Effects of heart rate variability biofeedback on EEG alpha asymmetry and anxiety symptoms in male athletes: a pilot study. Appl. Psychophysiol. Biofeedback 41, 141–150. [PubMed: 26459346]

Edlinger G, Guger C, 2005. Correlation changes of EEG and ECG after fast cable CAR ascents. Conf. Proc. IEEE Eng. Med. Biol. Soc 5, 5540–5543.

Eikelboom WS, Singleton E, van den Berg E, Coesmans M, Mattace Raso F, van Bruchem RL, Goudzwaard JA, de Jong FJ, Koopmanschap M, den Heijer T, Driesen JJM, Vroegindeweij L, Thomeer EC, Hoogers SE, Dijkstra AA, Zuidema SU, Pijnenburg YAL, Scheltens P, van Swieten JC, Ossenkoppele R, Papma JM, 2019. Early recognition and treatment of neuropsychiatric symptoms to improve quality of life in early Alzheimer's disease: protocol of the BEAT-IT study. Alzheimers Res. Ther 11, 48. [PubMed: 31122267]

Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM, 2007. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch. Neurol 64, 343–349. [PubMed: 17210801]

Fagan AM, Shaw LM, Xiong C, Vanderstichele H, Mintun MA, Trojanowski JQ, Coart E, Morris JC, Holtzman DM, 2011. Comparison of analytical platforms for cerebrospinal fluid measures of beta-amyloid 1–42, total tau, and p-tau181 for identifying Alzheimer disease amyloid plaque pathology. Arch. Neurol 68, 1137–1144. [PubMed: 21555603]

Forte G, De Pascalis V, Favieri F, Casagrande M, 2019a. Effects of blood pressure on cognitive performance: a systematic review. J. Clin. Med 9.

Forte G, Favieri F, Casagrande M, 2019b. Heart rate variability and cognitive function: a systematic review. Front. Neurosci 13, 710. [PubMed: 31354419]

Frewen J, Finucane C, Savva GM, Boyle G, Coen RF, Kenny RA, 2013. Cognitive function is associated with impaired heart rate variability in ageing adults: the Irish longitudinal study on ageing wave one results. Clin. Auton. Res 23, 313–323. [PubMed: 24077752]

Gladwin TE, de Jong R, 2005. Bursts of occipital theta and alpha amplitude preceding alternation and repetition trials in a task-switching experiment. Biol. Psychol. 68, 309–329. [PubMed: 15620797]

Goodfellow I, Bengio Y, Courville A, 2016. Deep Learning The MIT Press, Cambridge, Massachusetts.

Grabner RH, Fink A, Stipacek A, Neuper C, Neubauer AC, 2004. Intelligence and working memory systems: evidence of neural efficiency in alpha band ERD. Brain Res. Cogn. Brain Res 20, 212–225. [PubMed: 15183393]

Harrington MG, Chiang J, Pogoda JM, Gomez M, Thomas K, Marion SD, Miller KJ, Siddarth P, Yi X, Zhou F, Lee S, Arakaki X, Cowan RP, Tran T, Charleswell C, Ross BD, Fonteh AN, 2013. Executive function changes before memory in preclinical Alzheimer's pathology: a prospective, cross-sectional, case control study. PLoS One 8, e79378. [PubMed: 24260210]

Harrington MG, Edminster SP, Buennagel DP, Chiang JP, Sweeney MD, CHui HC, V, Z.B., Fonteh AN, 2019. Four-year longitudinal study of cognitively healthy individuals: CSF amyloid/tau levels and nanoparticle membranes identify high risk for Alzheimer's disease. Alzheimers Dement 15.

Hayano J, Yuda E, 2019. Pitfalls of assessment of autonomic function by heart rate variability. J. Physiol. Anthropol 38, 3. [PubMed: 30867063]

Hsieh S, Allport A, 1994. Shifting attention in a rapid visual search paradigm. Percept. Mot. Skills 79, 315–335. [PubMed: 7991326]

Hu L, Peng W, Valentini E, Zhang Z, Hu Y, 2013. Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. J. Pain 14, 89–99. [PubMed: 23273836]

Hutchison KA, Balota DA, Duchek JM, 2010. The utility of Stroop task switching as a marker for early-stage Alzheimer's disease. Psychol. Aging 25, 545–559. [PubMed: 20853964]

Issac TG, Chandra SR, Gupta N, Rukmani MR, Deepika S, Sathyaprabha TN, 2017. Autonomic dysfunction: a comparative study of patients with Alzheimer's and frontotemporal dementia - a pilot study. J. Neurosci. Rural Pract 8, 84–88. [PubMed: 28149088]

Jack CR Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Contributors, 2018. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 14, 535–562. [PubMed: 29653606]

Jandackova VK, Scholes S, Britton A, Steptoe A, 2016. Are changes in heart rate variability in middle-aged and older people normative or caused by pathological conditions? Findings from a large population-based longitudinal cohort study. J. Am. Heart Assoc 5.

Jersild AT, 1927. Mental Set and Shift (New York).

Kennelly SP, Lawlor BA, Kenny RA, 2009. Blood pressure and dementia - a comprehensive review. Ther. Adv. Neurol. Disord 2, 241–260. [PubMed: 21179532]

Kim DH, Lipsitz LA, Ferrucci L, Varadhan R, Guralnik JM, Carlson MC, Fleisher LA, Fried LP, Chaves PH, 2006. Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: Women's Health and Aging Study I. J. Am. Geriatr. Soc 54, 1751–1757. [PubMed: 17087704]

Klimesch W, 1996. Memory processes, brain oscillations and EEG synchronization. Int. J. Psychophysiol 24, 61–100. [PubMed: 8978436]

Klimesch W, 1997. EEG-alpha rhythms and memory processes. Int. J. Psychophysiol 26, 319–340. [PubMed: 9203012]

Klimesch W, 2012. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn. Sci 16, 606–617. [PubMed: 23141428]

Klimesch W, Doppelmayr M, Pachinger T, Russegger H, 1997. Event-related desynchronization in the alpha band and the processing of semantic information. Brain Res. Cogn. Brain Res 6, 83–94. [PubMed: 9450602]

Klimesch W, Sauseng P, Hanslmayr S, 2007. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res. Rev 53, 63–88. [PubMed: 16887192]

Krause CM, Lang AH, Laine M, Kuusisto M, Porn B, 1996. Event-related EEG desynchronization and synchronization during an auditory memory task. Electroencephalogr. Clin. Neurophysiol 98, 319–326. [PubMed: 8641153]

Laborde S, Mosley E, Mertgen A, 2018. Vagal tank theory: the three Rs of cardiac vagal control functioning - resting, reactivity, and recovery. Front. Neurosci 12, 458. [PubMed: 30042653]

Leuzy A, Heurling K, Ashton NJ, Scholl M, Zimmer ER, 2018. In vivo detection of Alzheimer's disease. Yale J. Biol. Med 91, 291–300. [PubMed: 30258316]

Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F, 2005. Poststroke dementia. Lancet Neurol 4, 752–759. [PubMed: 16239182]

Lin F, Ren P, Wang X, Anthony M, Tadin D, Heffner KL, 2017. Cortical thickness is associated with altered autonomic function in cognitively impaired and non-impaired older adults. J. Physiol. 595, 6969–6978. [PubMed: 28952161]

Magosso E, Ricci G, Ursino M, 2019. Modulation of brain alpha rhythm and heart rate variability by attention-related mechanisms. AIMS Neurosci 6, 1–24. [PubMed: 32341965]

Mielke MM, Okonkwo OC, Oishi K, Mori S, Tighe S, Miller MI, Ceritoglu C, Brown T, Albert M, Lyketsos CG, 2012. Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimers Dement 8, 105–113. [PubMed: 22404852]

Monsell S, 2003. Task switching. Trends Cogn. Sci 7, 134–140. [PubMed: 12639695]

Nakamura A, Cuesta P, Fernandez A, Arahata Y, Iwata K, Kuratsubo I, Bundo M, Hattori H, Sakurai T, Fukuda K, Washimi Y, Endo H, Takeda A, Diers K, Bajo R, Maestu F, Ito K, Kato T, 2018. Electromagnetic signatures of the preclinical and prodromal stages of Alzheimer's disease. Brain 141, 1470–1485. [PubMed: 29522156]

Nicolini P, Ciulla MM, Malfatto G, Abbate C, Mari D, Rossi PD, Pettenuzzo E, Magrini F, Consonni D, Lombardi F, 2014. Autonomic dysfunction in mild cognitive impairment: evidence from power spectral analysis of heart rate variability in a cross-sectional case-control study. PLoS One 9, e96656. [PubMed: 24801520]

Nicolini P, Mari D, Abbate C, Inglese S, Bertagnoli L, Tomasini E, Rossi PD, Lombardi F, 2020. Autonomic function in amnestic and non-amnestic mild cognitive impairment: spectral heart rate variability analysis provides evidence for a brain-heart axis. Sci. Rep 10, 11661. [PubMed: 32669640]

Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A, 1997. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 28, 316–321. [PubMed: 9040682]

Pagano S, Fait E, Monti A, Brignani D, Mazza V, 2015. Electrophysiological correlates of subitizing in healthy aging. PLoS One 10, e0131063. [PubMed: 26098959]

Pettigrew C, Martin RC, 2016. The role of working memory capacity and interference resolution mechanisms in task switching. Q. J. Exp. Psychol. (Hove) 69, 2431–2451. [PubMed: 26594895]

Pfurtscheller G, Aranibar A, 1977. Event-related cortical desynchronization detected by power measurements of scalp EEG. Electroencephalogr. Clin. Neurophysiol 42, 817–826. [PubMed: 67933]

Pfurtscheller G, Klimesch W, 1992. Functional topography during a visuoverbal judgment task studied with event-related desynchronization mapping. J. Clin. Neurophysiol 9, 120–131. [PubMed: 1552000]

Pfurtscheller G, Lopes da Silva FH, 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol 110, 1842–1857. [PubMed: 10576479]

Prinsloo GE, Rauch HG, Karpul D, Derman WE, 2013. The effect of a single session of short duration heart rate variability biofeedback on EEG: a pilot study. Appl. Psychophysiol. Biofeedback 38, 45–56. [PubMed: 23129056]

Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S, 2017. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev 3, CD010803. [PubMed: 28328043]

Sauseng P, Klimesch W, Freunberger R, Pecherstorfer T, Hanslmayr S, Doppelmayr M, 2006. Relevance of EEG alpha and theta oscillations during task switching. Exp. Brain Res 170, 295–301. [PubMed: 16317574]

Sawilowsky S, 2009. New effect size rules of thumb. J. Mod. Appl. Stat. Methods 8, 8.

Schneider DW, 2015. Attentional control of response selection in task switching. J. Exp. Psychol. Hum. Percept. Perform 41, 1315–1324. [PubMed: 26076177]

Shaffer F, Meehan ZM, 2020. A practical guide to resonance frequency assessment for heart rate variability biofeedback. Front. Neurosci 14, 570400. [PubMed: 33117119]

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr., Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH, 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 280–292. [PubMed: 21514248]

Sullivan MP, Faust ME, 1993. Evidence for identity inhibition during selective attention in old adults. Psychol. Aging 8, 589–598. [PubMed: 8292287]

Thayer JF, Lane RD, 2009. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci. Biobehav. Rev 33, 81–88. [PubMed: 18771686]

Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH, 2009. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med 37, 141–153. [PubMed: 19424767]

Vazquez-Marrufo M, Galvao-Carmona A, Benitez Lugo ML, Ruiz-Pena JL, Borges Guerra M, Izquierdo Ayuso G, 2017. Retest reliability of individual alpha ERD topography assessed by human electroencephalography. PLoS One 12, e0187244. [PubMed: 29088307]

Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM, Rotterdam Scan S, 2003a. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 34, 1126–1129. [PubMed: 12690219]

Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM, 2003b. Silent brain infarcts and the risk of dementia and cognitive decline. N. Engl. J. Med 348, 1215–1222. [PubMed: 12660385]

Verstraeten E, Cluydts R, 2002. Attentional switching-related human EEG alpha oscillations. Neuroreport 13, 681–684. [PubMed: 11973470]

Watanabe N, Reece J, Polus BI, 2007. Effects of body position on autonomic regulation of cardiovascular function in young, healthy adults. Chiropr. Osteopat 15, 19. [PubMed: 18045493]

Wu S, Hitchman G, Tan J, Zhao Y, Tang D, Wang L, Chen A, 2015. The neural dynamic mechanisms of asymmetric switch costs in a combined Stroop-task-switching paradigm. Sci. Rep 5, 10240. [PubMed: 25989933]

Wutzl B, Golaszewski SM, Leibnitz K, Langthaler PB, Kunz AB, Leis S, Schwenker K, Thomschewski A, Bergmann J, Trinka E, 2021. Narrative review: quantitative EEG in disorders of consciousness. Brain Sci 11.

Yeung N, Monsell S, 2003. Switching between tasks of unequal familiarity: the role of stimulus-attribute and response-set selection. J. Exp. Psychol. Hum. Percept. Perform 29, 455–469. [PubMed: 12760628]

Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, Donati P, De Vecchi M, Romanelli G, Grassi V, Padovani A, 2005. QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. J. Am. Geriatr. Soc 53, 2135–2139. [PubMed: 16398898]

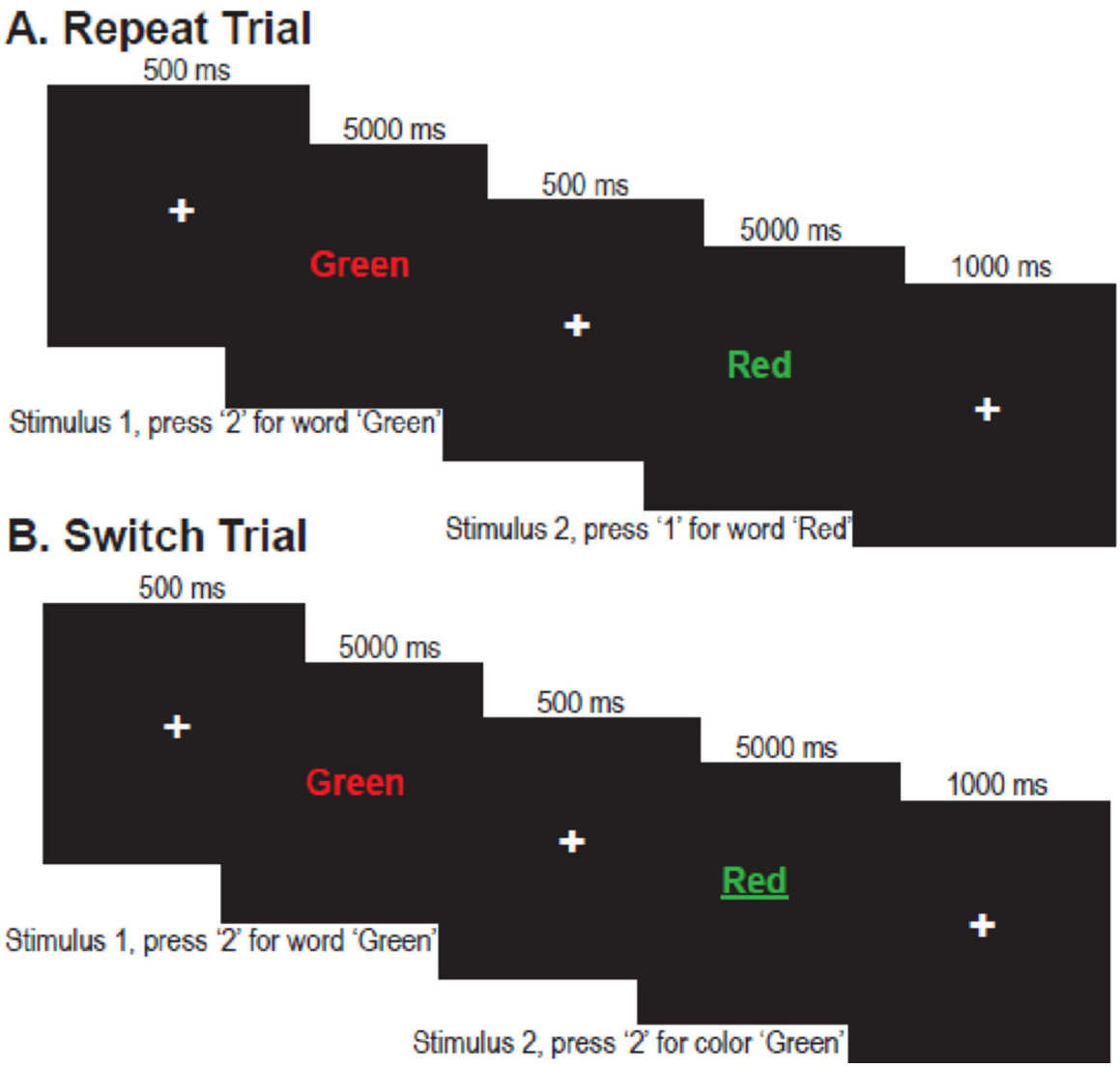

Fig. 1.

Task switching testing paradigms. Each trial includes two sequential stimuli. Each stimulus is incongruent colored word. Participants were requested to respond to the word itself (no-underline), or to the color of the ink (underlined), by press a button ('1' for red, '2' for green). Tasks include random mixture of low load repeat trials (A) or high load switch trials (B).

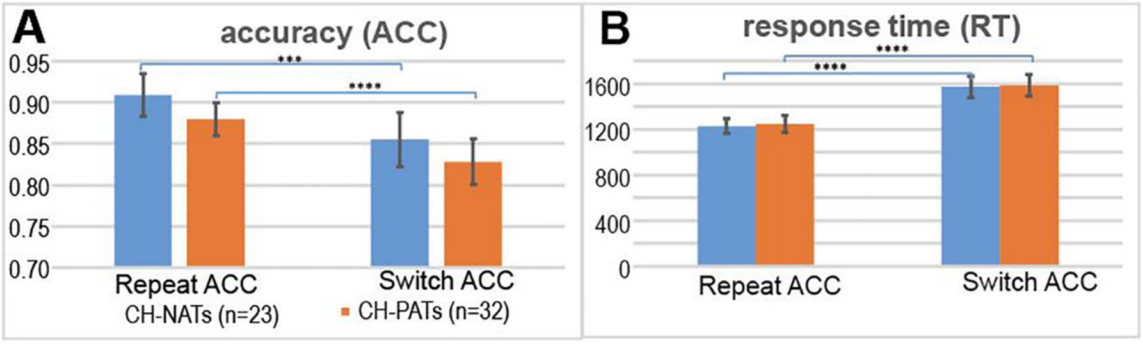

Fig. 2.

Behavioral responses of task switching. A) The accuracy (ACC) was not different between CH-NATs and CH-PATs. ACC during high load switch trials was lower than during low load repeat trials, in both groups. B) The response time (RT) was not different between CH-NATs and CH-PATs. RT during high load switch trials was longer than during low load repeat trials, in both groups.

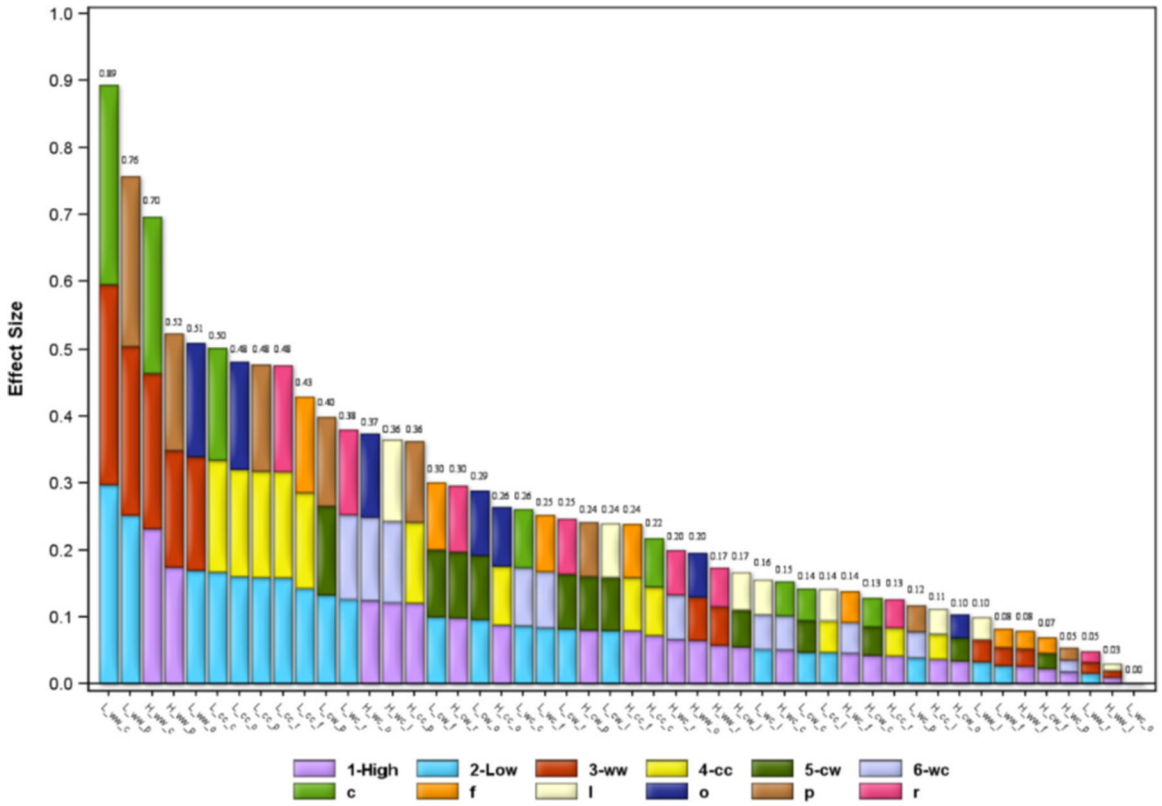

Fig. 3.

Summary of effect sizes by Cohen's d. Effect sizes for all comparisons were ranked including all combinations of: trial types (wW (3-ww), cC (4-cc), cW (5-cw), or wC (6-wc)), alpha power (low alpha (2-Low) or high alpha (1-High)), regions (F (f), C (c), P (p), LT (l), RT (r), or O (o)). Cohen's d values were indicated at the top of each combination.

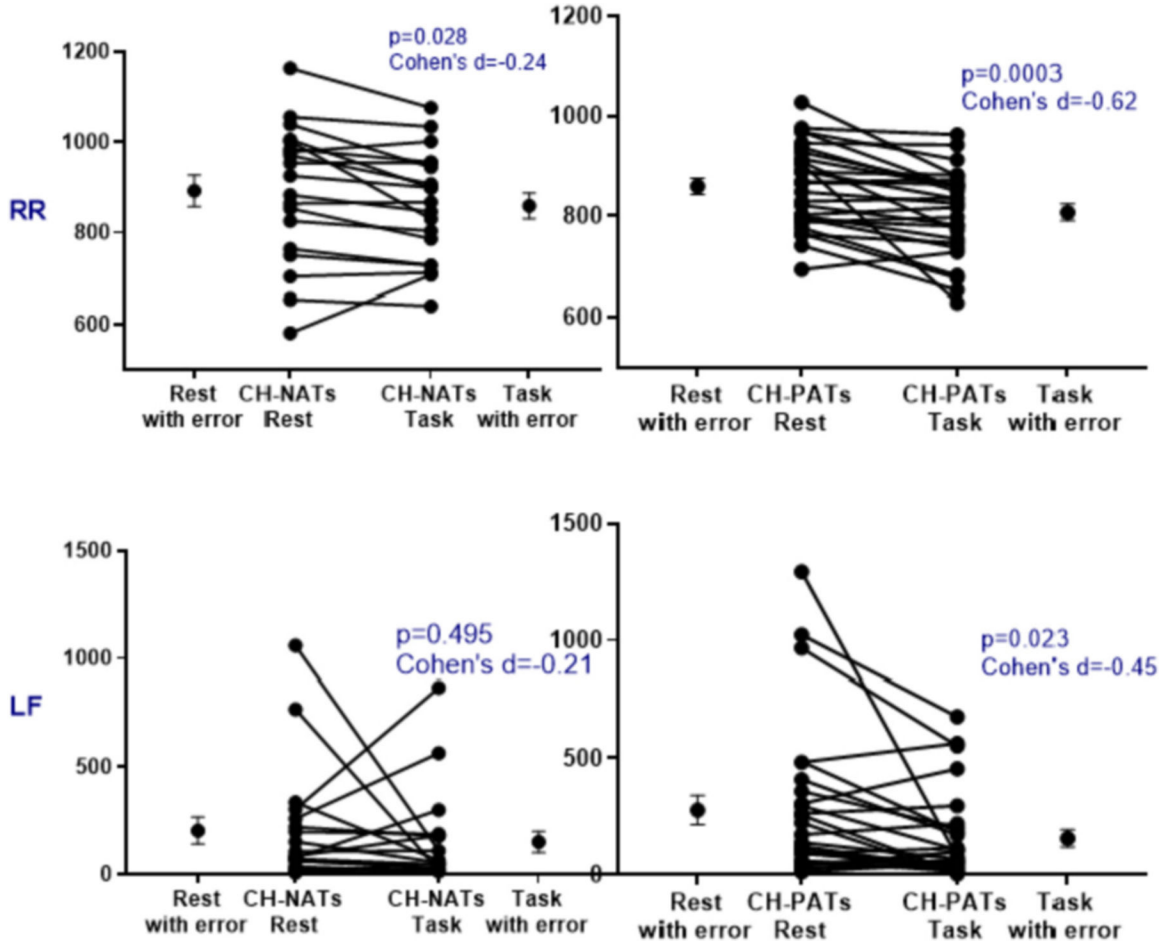

Fig. 4.

HRV comparisons between resting state and task switching in CH-NATs and CH-PATs. A) RR interval were reduced during the task than resting with medium effect size in CH-PATs, but not in CH-NATs; B) LF were reduced only in CH-PATs.

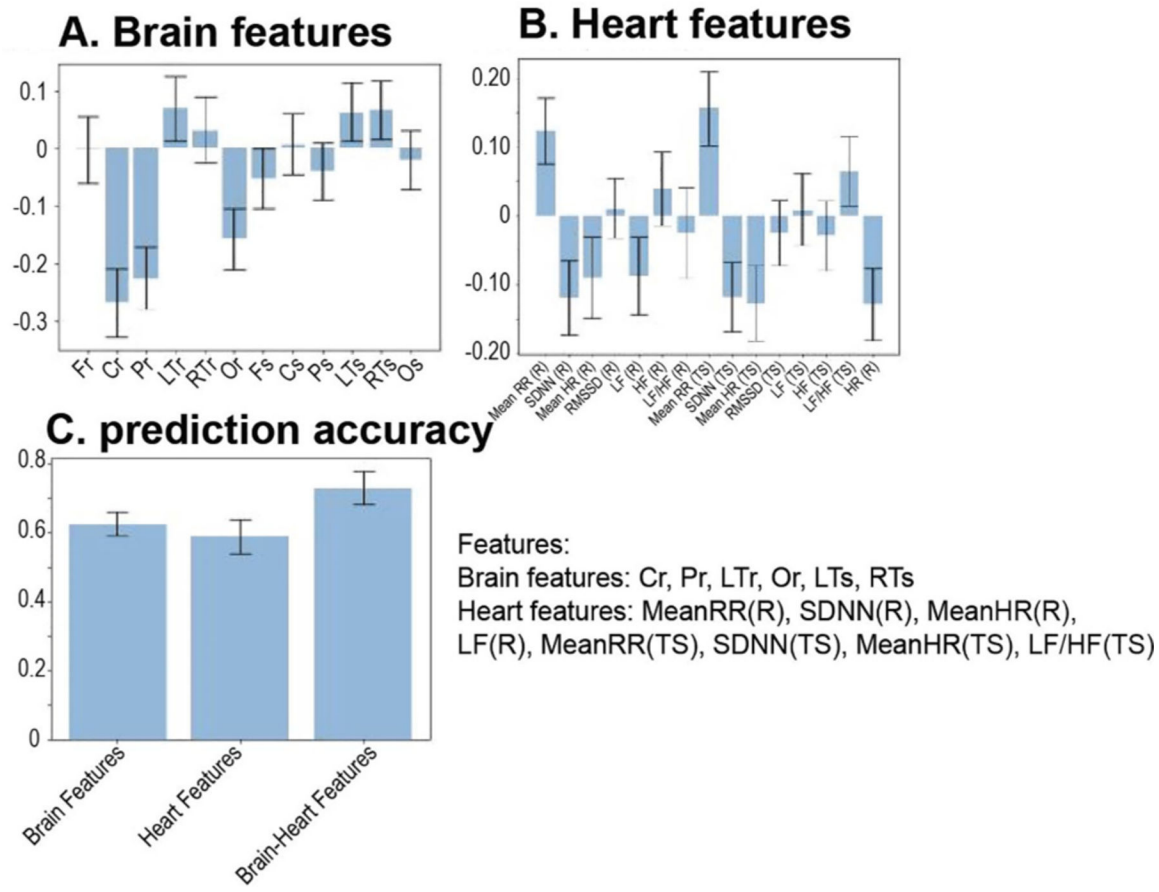

Fig. 5.

Machine learning analysis for the task switching challenge suggests HRV improves qEEG classification of CH-NATs and CH-PATs. A) Low alpha ERD on frontal (F), central (C), parietal (P), left temporal (LT), right temporal (RT), and occipital (O) regions were listed during repeat trials (r) and switch trials (s), and six low alpha features (Cr, Pr, LTr, Or, LTs, RTs) were considered brain features; B) HRV measures were listed during resting state (R) and task switching (TS) and nine HRV features (MeanRR(R), SDNN(R), MeanHR(R), LF (R), MeanRR(TS), SDNN(TS), MeanHR(TS), LF/HF(TS), HR(R)) were considered heart features; C) using two-layer fully-connected neural network, HRV can improve brain features' test accuracy from 0.64 ± 0.04 to 0.71 ± 0.04. On the other hand, the heart feature can also achieve 0.62 ± 0.04 accuracy. The experiment is conducted 50 times with random split of training (80%) and testing (20%) data.

Table 1

Low and high alpha powers for both CH-NATs and CH-PATs during repeat trials. Significance was estimated using effect size (ES) under Cohen's criteria.

Repeat	Low alpha (8–11 Hz)						
	NAT		PAT		p-value	95% CI	Cohen's d
Regions	Ave	SD	Ave	SD			
F	−0.90	1.00	−0.60	0.92	0.307	(−0.28, 0.90)	0.31
C	−0.72	0.72	−0.18	0.66	**0.011**	(0.18, 1.40)	**0.79**
P	−0.83	0.92	−0.25	0.75	**0.024**	(0.09, 1.30)	**0.70**
LT	−0.70	0.79	−0.59	0.88	0.658	(−0.45, 0.72)	0.13
RT	−0.65	0.66	−0.48	0.77	0.436	(−0.35, 0.82)	0.24
O	−0.64	0.85	−0.14	0.95	0.071	(−0.04, 1.15)	0.55
Repeat	High alpha (11–13 Hz)						
	NAT		PAT		p-value	95% CI	Cohen's d
Regions	Ave	SD	Ave	SD			
F	−0.90	1.06	−0.80	0.99	0.735	(−0.49, 0.69)	0.10
C	−0.75	0.89	−0.36	0.82	0.134	(−0.14, 1.05)	0.46
P	−0.90	0.96	−0.44	1.00	0.129	(−0.13, 1.06)	0.46
LT	−0.56	0.79	−0.59	0.84	0.884	(−0.63, 0.54)	−0.04
RT	−0.59	0.69	−0.61	0.80	0.916	(−0.62, 0.56)	−0.03
O	−0.78	0.97	−0.54	0.95	0.410	(−0.34, 0.84)	0.25

CI: confidence interval. Bold: $p < 0.05$ or Cohen's $d > 0.5$.

Table 2

Low and high alpha powers for both CH-NATs and CH-PATs for word switch cost (cW-wW). Significance was estimated using Effect Size (ES) under Cohen's Criteria.

Repeat	**Low alpha (8–11 Hz)**						
	NAT		**PAT**		**p-value**	**95% CI**	**Cohen's d**
Regions	**Ave**	**SD**	**Ave**	**SD**			
F	0.15	0.97	0.34	0.90	0.491	(−0.38, 0.80)	0.21
C	0.43	0.68	−0.12	0.66	**0.008**	(−1.44, −0.22)	**−0.83**
P	0.23	1.13	−0.03	0.79	0.366	(−0.86, 0.32)	−0.27
LT	0.34	0.74	0.44	1.28	0.755	(−0.49, 0.68)	0.09
RT	0.23	0.78	0.04	0.69	0.406	(−0.84, 0.34)	−0.25
O	0.09	1.03	0.12	1.03	0.496	(−0.79, 0.38)	−0.21
Repeat	**High alpha (11–13 Hz)**						
	NAT		**PAT**		**p-value**	**95% CI**	**Cohen's d**
Regions	**Ave**	**SD**	**Ave**	**SD**			
F	0.09	0.92	0.24	0.78	0.560	(−0.41, 0.76)	0.18
C	0.32	0.74	−0.12	0.49	**0.019**	(−1.34, −0.13)	**−0.73**
P	0.00	0.91	−0.22	0.73	0.359	(−0.87, 0.31)	−0.28
LT	0.12	0.61	0.25	1.09	0.647	(−0.45, 0.73)	0.14
RT	0.06	0.83	−0.06	0.61	0.572	(−0.76, 0.42)	−0.17
O	−0.05	0.98	−0.14	1.09	0.774	(−0.67, 0.50)	−0.09

CI: confidence interval. Bold: $p < 0.05$ or Cohen's $d > 0.5$.

Table 3

Effect of Task Switching on HRV.

CH-NATs			**p/Cohen's d**
HRV	**Rest**	**Task**	**Task vs. rest**
RR	892.4 (34.5)	859.0 (27.9)	0.028/−0.24 *
SDNN	19.3 (2.9)	18.3 (3.2)	0.64/−0.08
RMSSD	21.3 (4.2)	21.5 (5.0)	0.949/0.01
LF-HRV	203.5 (62.7)	150.8 (50.4)	0.495/−0.21
HF-HRV	228.7 (111.0)	214.3 (128.5)	0.789/−0.03
LF/HF-HRV	4.3 (2.3)	2.0 (0.5)	0.344/−0.31
CH-NATs			**p/Cohen's d**
HRV	**Rest**	**Task**	**Task vs. rest**
RR	859.1 (16.2)	806.6 (16.6)	0.0003/−0.62 *
SDNN	23.5 (2.8)	20.1 (2.8)	0.091/−0.23
RMSSD	24.2 (4.1)	22.9 (4.1)	0.628/−0.06
LF-HRV	278.4 (63.3)	157.5 (36.5)	0.023/−0.45 *
HF-HRV	279.1 (118.4)	250.3 (134.7)	0.285/−0.04
LF/HF-HRV	6.2 (3.8)	1.5 (0.2)	0.229/−0.33

* $p < 0.05$.